Identification and Management of Neonatal Hypoglycaemia in Term and Late-preterm (> 34 weeks) Infants

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The North West Neonatal Network (NWNODN) consists of 3 locality neonatal networks, Cheshire and Merseyside (CM) Lancashire and South Cumbria (LSC) and Greater Manchester (GM). This document has agreed by locality Clinical Effective Groups (CEG) and can be adapted for local use. **Please acknowledge source if this document is adapted for local use.**	

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Background

In healthy term infants, it is normal for blood glucose levels to fall immediately after birth and then rise again in the next few hours either spontaneously or after feeding. Blood glucose concentrations may therefore normally be low in the first few days of life in *asymptomatic*, healthy, well grown babies and this does not appear to be associated with any adverse consequences [1,2].

In contrast, symptomatic hypoglycaemia (particularly if associated with hypoglycaemic seizures) carries a high risk of subsequent neurodevelopmental impairment [3]. Severe and/or prolonged hypoglycaemia is also known to be associated with transient neurophysiological abnormality and structural changes in the brain.

The aim of this guideline is to identify babies at risk of developing hypoglycaemia, to prevent the development of severe and/or symptomatic hypoglycaemia and to provide guidance on the investigation and treatment of hypoglycaemic babies.

Definition

It is impossible to define a single value of plasma glucose below which brain injury ('neuroglycopaenia') occurs in newborn babies. Injury is likely to vary depending on the severity and duration of hypoglycaemia as well as the individual's ability to respond and make appropriate metabolic adaptations.

Historically, a single cut-off value of < 2.6 mmol/L was often used to define hypoglycaemia primarily based on an association with adverse long-term neurodevelopmental outcome in low birth weight babies. However, a number of high quality recent studies have failed to demonstrate any such relationship [4,5]. Other studies have suggested that only a lower threshold of < 1.7 or < 2.2 mmol/L is likely to be harmful [6,7].

In recognition of this uncertainty, 'operational thresholds' for neonatal hypoglycaemia at which intervention should be considered have been suggested [8,13]:

- A single measurement of blood glucose < 1 mmol/L;
- A persistently low blood glucose < 2 mmol/L in an asymptomatic baby;
- A single measurement of < 2.5 mmol/L in a symptomatic baby.

Summary of Evidence

There are few randomised controlled trials to guide the clinical management of babies at-risk of, or with established, hypoglycaemia [9-11]. Furthermore, the results from existing clinical studies are difficult to interpret because of factors such as variation in methods of blood glucose measurement, inconsistent definitions of hypoglycaemia, and the lack of data regarding long-term outcomes. The recommendations outlined below are primarily based on consensus statements (specifically from the BAPM Framework of Practice) and expert opinion [13-16].

Blood glucose measurement- which babies?

Blood glucose concentration should only be measured routinely in the following two groups of babies:

1. Babies at risk of developing hypoglycaemia:
a) Small for gestational age (birth weight < 2nd centile, GROW or WHO centiles)
b) Preterm babies < 37 weeks' gestation
c) Infants of diabetic mothers (all types of diabetes)
d) Babies whose mothers have received beta-blockers (in the third trimester or at time of delivery)
e) Babies born following fetal acidaemia (cord pH < 7, BE < -12)
f) Babies born to families with a history of metabolic disorder (e.g. MCADD)
g) Suspected/proven sepsis
h) Hypothermia (< 36.5°C)

2. Babies with signs potentially attributable to hypoglycaemia:
a) Cyanosis
b) Apnoea
c) Altered level of consciousness
d) Seizures
e) Hypotonia
f) Lethargy
g) High-pitched cry
h) Abnormal feeding behaviour*

Jitteriness, defined as excessive repetitive movements of one or more limbs, which are unprovoked and not in response to a stimulus, is common and is not by itself an indication to measure blood glucose.

*Abnormal feeding behaviour (not waking for feeds, not sucking effectively, appearing unsettled and demanding very frequent feeds), especially *after a period of feeding well* may be indicative of hypoglycaemia. It should prompt a full clinical assessment and consideration of blood glucose measurement.

Blood glucose measurement – which method?

Accurate measurement of blood glucose level is essential for diagnosis and management of neonatal hypoglycaemia. Current cot side technology is prone to significant inaccuracy, particularly in the range 0 – 2 mmol/l. The blood gas biosensor (which uses a blood glucose electrode system) should be considered the reference standard for measuring whole blood glucose based on accuracy and speed of result availability. Do not use near-patient testing devices such as the Hemocue machine as the sole means of identifying hypoglycaemia. No baby should be admitted to the neonatal unit for treatment of hypoglycaemia unless a member of the neonatal staff (doctor, ANNP or TC/neonatal nurse) has performed a blood glucose measurement on the blood gas machine. This must take place before the mother and baby are separated.

Management of babies at-risk of hypoglycaemia (Flow Chart A)

Follow the guidance given in Flow Chart A.

A Hypoglycaemia Care Pathway Document should be started on the labour ward by a member of the paediatric team and placed in the baby's case notes. Document that the baby is at-risk of hypoglycaemia in the postnatal ward transfer form.

Key practice points:

- Provide parents with verbal and written information that explains why their baby is receiving extra support and why blood glucose monitoring is being performed. This information should ideally be given in the antenatal period, if appropriate.
- Immediately after delivery, dry and put a hat on the baby. Ensure the room is warm and draught-free. Offer mother skin-to-skin contact with her baby.
- Commence observations using the NEWS Chart (3 hourly) and continue until two consecutive blood glucose concentrations > 2.5 mmol/l have been obtained.
- Offer an early breast or bottle feed within the first 60 minutes. For women who choose to formula feed, offer 10-15 ml/kg within the first hour and plan to give at least 80 ml/kg/day. Provide feeding support and document feeding effectiveness.
- Offer breast/bottle feeds in response to feeding cues as often as possible and at least 3-hourly.
- If the baby is not showing signs of effective breastfeeding, maximise breast milk supply by encouraging continuous skin-to-skin contact and teaching the mother to hand express. Continue to support milk expression at least 8-10 times per 24-hour period.
- Any colostrum expressed should be given to the baby immediately. If no/minimal colostrum is available and after discussion with the mother, consider supplementing with formula milk until colostrum is available.
- Measure blood glucose level before the second feed and between 2-4 hours after birth.
- Do not transfer babies at-risk of hypoglycaemia to community care before you are satisfied that the baby is maintaining blood glucose levels > 2.5 mmol/l on at least two consecutive occasions and is feeding well. Infants of diabetic mothers should not be discharged until they are at least 24 hours old.
- If the pre-feed BG remains 2-2.4 mmol/L on more than two occasions, contact TC team for further advice and support.

Management of babies with established hypoglycaemia (Flow Charts B, C)

Based on the result of the first blood glucose (BG) measurement, place the baby on one of the following care pathways:

Flow Chart B: First (pre-second feed) BG 1 – 1.9 mmol/l and no abnormal signs

Flow Chart C: First (pre-second feed) BG < 1 mmol/l, persistently low BG 1-1.9 mmol/l and/or clinical signs consistent with hypoglycaemia and BG < 2.5 mmol/l.

Flow Chart B: Key practice points:

If a baby has asymptomatic hypoglycaemia with a BG of 1 – 1.9 mmol/l:

- Request paediatric review
- Administer 200 mg/kg of 40% buccal glucose gel (0.5 ml/kg - refer to pharmacy data sheet) alongside feeding support.
- Offer another breast/bottle feed immediately after administering glucose gel:
  - If a baby is not breastfeeding effectively, aim to give at least 10 ml/kg of expressed milk. If no/insufficient expressed breast milk available, supplement with an equivalent volume of formula milk (after discussion with the mother).
  - If bottle feeding, aim to give at least 10 ml/kg of formula milk.
- Recheck BG concentration 30-60 minutes after gel administration.
- If BG remains between 1-2.4 mmol/L, offer a second dose of glucose gel (maximum two doses only) and re-check BG concentration 30-60 minutes after gel administration.
- If BG remains between 1-2.4 mmol/L despite two doses of glucose gel, admit to the neonatal unit and follow Flow Chart C.
- If BG > 2.5 mmol/L, continue to support feeding by feeding in response to feeding cues as often as possible and at least 3-hourly.
- Discontinue glucose monitoring once two consecutive pre-feed BG measurements are > 2.5 mmol/L and if the baby remains asymptomatic.

Flow Chart C: Key practice points:

If a baby has severe hypoglycaemia (BG < 1 mmol/l) or persistently mild-moderate hypoglycaemia (BG 1- 2.4 mmol/l) and/or clinical signs attributable to hypoglycaemia:

- Request urgent paediatric review.
- Admit to the neonatal unit for hypoglycaemia 'screening' blood samples and intravenous glucose.
- If intravenous access has been obtained, take screening blood samples and give 2.5 ml/kg of IV glucose 10% followed by an infusion of 60 ml/kg/day.
- If attempts at establishing intravenous access are unsuccessful, give 200 mg/kg (0.5 ml/kg) of 40% buccal glucose gel followed by glucagon 200 micrograms/kg (max. 1 mg as single dose), if necessary. This should be only treated as an interim measure while intravenous access is being secured.
- Continue enteral feeding (at least 3-hourly by mouth or tube, as appropriate) up to a maximal total fluid intake of 120 ml/kg/day, unless the baby is vomiting or there are other contraindications.
- Recheck BG concentration 30-60 minutes after giving IV glucose or glucose gel.
  - If BG < 1 mmol/l or symptomatic: give a further 2.5 ml/kg IV bolus of 10% glucose and increase glucose delivery by 2 mg/kg/min (see table 1). Recheck BG concentration in 30-60 minutes. Repeat cycle until BG improves.
  - If BG 1 – 2.4 mmol/l: increase glucose delivery by 2 mg/kg/min. Recheck BG concentration in 30-60 minutes. Repeat cycle until BG improves.
  - If BG > 2.5 mmol/l: slowly wean IV glucose infusion. Continue BG monitoring until baby is fully enterally fed and BG > 2.5 mmol/L (or 3.5 mmol if hyperinsulinaemic) for at least 24 hours.

Investigation of hypoglycaemia

A newborn with persistent (more than 2 measurements < 2 mmol/l within the first 48 hours after birth) or severe hypoglycaemia (< 1 mmol/l at any time), and infants with signs of acute neurological dysfunction and blood glucose < 2.5 mmol/l should have the following investigations performed during the period of hypoglycaemia, after discussion with a Consultant:

- First-line investigations (prior to starting IV glucose infusion) - Consider evaluation for early-onset sepsis, blood glucose, blood gas, insulin, c-peptide, cortisol, growth hormone, fatty acids, ketone bodies, ammonia.
- Second-line investigations - Serum for amino acids, pyruvate, carnitine, acyl carnitine profile; Urine for amino acids, organic acids and ketones.

Hyperinsulinism should also be considered if the blood glucose concentration remains low (< 2 mmol/l on three or more occasions in first 48 hours despite adequate energy provision and feeding plan), or if a glucose intake greater than 8 mg/kg/min is required to maintain BG > 3.5 mmol/l in the first week after birth. In cases of suspected or confirmed hyperinsulinism, aim to maintain the blood glucose concentration > 3 mmol/l (if < 48 hours old) or > 3.5 mmol/l (if > 48 hours old).

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Table 1 - Calculation of intravenous glucose administration rates (mg/kg/min) from standard glucose infusions*

	GLUCOSE INFUSION CONCENTRATION			
INFUSION RATE (ml/kg/day)	**10%** (100 mg/ml)	**12.5%** (125 mg/ml)	**15% (150 mg/ml)**	**20% (200 mg/ml)**
60	4.2	5.2	6.3	8.3
75	5.2	6.5	7.8	10.4
90	6.3	7.8	9.4	12.5
120	8.3	10.4	12.5	16.7
150	10.4	13	15.6	20.8

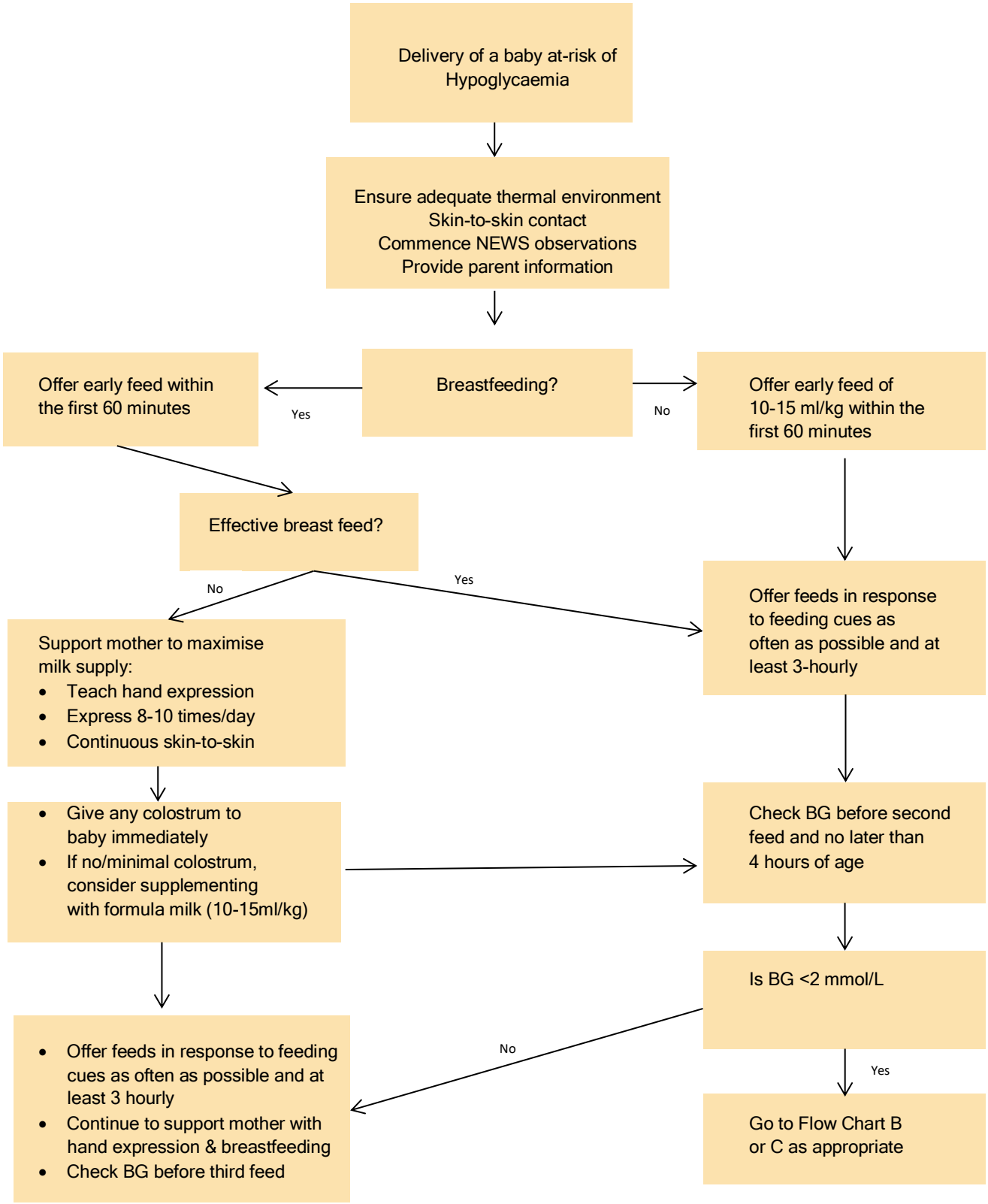
NB. Glucose intake (mg/kg/min) = % glucose x [Daily fluid intake (ml/kg/day)/144]

* Aim to increase intravenous glucose intake in steps of ~ 2 mg/kg/minute, initially by increasing the infusion rate up to the maximum daily intake (e.g. 120 ml/kg/day), and subsequently by increasing the concentration of glucose being infused.

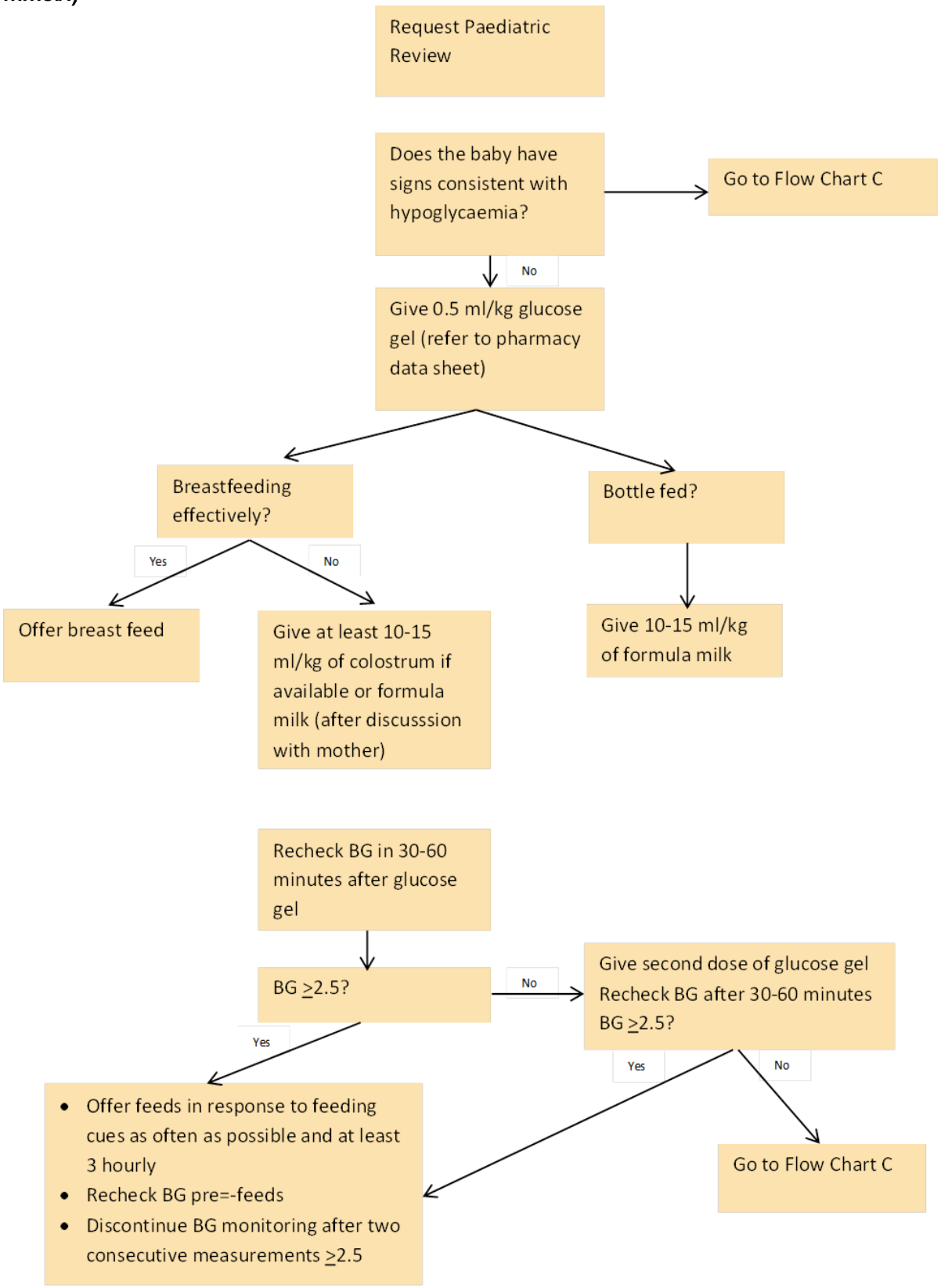
Regimen for weaning an intravenous glucose infusion

1. Start weaning intravenous glucose intake once pre-feed BG is > 2.5 mmol/l on two consecutive occasions.
2. Initially, wean concentration of glucose (e.g. from 15% to 12.5%).
3. Repeat pre-feed BG within 2 hours of weaning concentration of glucose.
4. Once two pre-feed BG are > 2.5 mmol/l, continue to wean concentration of glucose until baby is receiving 10% glucose.
5. Thereafter, once two pre-feed BG are > 2.5 mmol/l, wean infusion rate in steps of 20 ml/kg/day every 6 hours until normal daily fluid intake is reached
6. Check pre-feed BG within 2 hours of weaning intravenous glucose intake.

Flow Chart A - Management of babies at-risk of hypoglycaemia



Flow Chart B - Management of babies with mild-moderate hypoglycaemia (pre-feed BG 1-1.9 mmol/l)



Flow Chart C - Management of babies with severe hypoglycaemia (pre-feed BG < 1 mmol/l), persistent mild-moderate hypoglycaemia (pre-feed BG 1 - 2.4 mmol/l) and/or clinical signs consistent with hypoglycaemia and BG < 2.5 mmol/l